Claim 11 has been amended to replace "consisting essentially of" with "comprising". Claim 12 has been amended to recite "consisting of". Claim 13 has been amended to recite "consisting of". These amendments introduce no new matter.

Claim 22 has been amended to recite "protein of SEQ ID NO: 2". Support for this amendment is found throughout specification, for example, on page 10, line 8 and on page 60, line 6. Claim 22 has also been amended to recite "biological activity of polypeptides of SEQ ID NO: 3 or SEQ ID NO: 9". Support is found, for example, on page 59, lines 9-16 and page 28, lines 10-12.

Claims 44-46 have been amended to replace "wherein said nucleic acid molecule does not naturally comprise" with "wherein said nucleic acid is heterologous".

New Claims 54-61 have been added.

New Claim 54 has been added which is drawn to the amino acid sequence consisting of positions 1-7 of SEQ ID NO: 22. New Claim 55-57 have been added which are drawn to a nucleic acid that encodes a functional fragment of SEQ ID NO: 22 by virtue of comprising functional motifs of SEQ ID NO: 3 or SEQ ID NO: 9. Support can be found throughout the specification, for example, on page 16, line 26 *et seq*.

New Claim 58 has been added which is drawn to a method of preparing a fragment of protein of SEQ ID NO: 2, comprising polypeptides of SEQ ID NO: 3 or SEQ ID NO: 9. Support can be found throughout specification, for example, on page 2, line 25.

New Claims 59-61 have been added which are drawn to a nucleic acid encoding a protein of SEQ ID NO: 2 or a functional fragment thereof, wherein said activity is binding to a CD2 molecule. Support can be found, for example, at page 30, line 15.

Additional remarks addressing the issues raised in the Office Action are presented below under the appropriate subheading.

Oath/Declaration

The Examiner's comment regarding the Declaration is noted. A Supplemental Declaration is being filed concurrently.

Objection to the Specification

The specification has been amended as follows to address the objections raised by the Examiner:

A) The hyperlink on page 27, line 24 has been deleted.

B) The omission of "SEQ ID NOS:" for the sequences that require them under 37 C.F.R. §§1.821-1.825 has been corrected. Applicants are also submitting a Substitute Sequence Listing concurrently herewith.

Drawings

It is noted that the Examiner's file is missing the color drawings. The color drawings are being re-submitted concurrently herewith, along with a Petition to Accept Color Drawings.

Claim Objections

The Examiner objects to Claim 7-13 because of the absence of an article modifying the subject noun. Claims 7-13 have been amended as requested by the Examiner.

Rejection of Claims 7-22 and 44-46 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected Claims 7-22 and 44-46 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

A) Claims 7-9, 14, 18, and 22 are rejected as indefinite in their recitation of the phrase "nucleic acid molecule which encodes" because, the Examiner alleges, it is unclear whether closed or open language is intended. The Examiner invites Applicants to clarify.

Claim 7 has been amended to recite an isolated nucleic acid molecule which encodes a protein comprising SEQ ID NO: 2 or a fragment thereof as recited in the claim, or the complement of said nucleic acid molecule. Claims 8, 9, 14, 18, and 22 are dependent on Claim 7 and should, therefore, be construed to encompass the limitations of Claim 7. The amendment makes clear that the language of the claim is open language.

B) Claim 8 is rejected as indefinite due to its recitation of the phrase "substantial sequence identity". The Examiner alleges that this phrase is not clearly defined in the specification. Applicants are invited to clarify.

Claim 8 has been amended to recite the phrase "sequence identity of at least 80%" in reference to a nucleic acid. The ranges of sequence identity are recited on page 27, lines 1-5; lines 14-27 describe the algorithm used by Applicants to ascertain said sequence identity. Applicants submit that the reference to a functional algorithm coupled with the definition of the "sequence identity" adequately define, describe and enable one skilled in the art to practice the invention of Claim 8 as amended.

C) Claims 11-13 and Claims 15-17 and 19-21 dependent thereon, and Claims 44-46 are rejected as indefinite due to recitation of the phrase "consisting essentially of a nucleotide sequence" because, the Examiner alleges, it is not clear whether closed or open language is intended.

Applicants believe that the reference to Claims 44-46 in this regard is an inadvertent error, because the phrase "consisting essentially of a nucleotide sequence" is not recited in these claims.

Claim 11 has been amended to recite "comprising". Claims 12 and 13 have been amended to recite "consisting of". Claims 15-17 are dependent on Claims 11-13 and should, therefore, be construed to encompass the recitations of Claims 11-13 as well as any additional elements these claims may have.

D) Claims 11-13 and Claims 15-17 and 19-21 dependent thereon are rejected as indefinite in their recitation of the phrase "sequence encoding the amino acid sequence". The Examiner alleges that it is not clear whether closed or open language is intended.

Applicants note that Claims 44-46 also recite the phrase "sequence encoding the amino acid sequence".

Claims 11-13, 15-17, 19-21, and 44-46 recite "nucleotide sequence encoding the amino acid sequence" of particular identified SEQ ID NOS. This recitation encompasses all *nucleotide*

sequences that, when translated, result in the specified amino acid sequence. As its subject matter, Claims 11-13, 15-17, 19-21, and 44-46 are drawn to "[a]n isolated *nucleic acid molecule*" (emphasis added). Said molecule may either *comprise* (as in Claims 11, 15 -17, 19 - 21, and 44 - 46) or *consist of* (as in Claims 12 and 13) a "nucleotide sequence encoding the amino acid sequence". Applicants believe that the language of these claims is clear on its face; if this rejection is maintained, clarification is respectfully requested.

E) The Examiner notes a discrepancy between SEQ ID NO: 9 as presented in the application and SEQ ID NO: 9 as presented in the Sequence Listing and states that this discrepancy renders Claims 12, 16 and 20 unclear. Applicants are submitting a Substitute Sequence Listing concurrently herewith, obviating this portion of the rejection.

F) Claim 9 is rejected for the lack of antecedent basis for the recitation of the limitation "endogenous gene". Claim 9 has been amended to recite "an endogenous gene".

G) Claims 44-46 are rejected in their recitation of the phrase "naturally comprise" because, the Examiner states, it is unclear what is encompassed by said phrase.

Claims 44-46 have been amended to recite "wherein said nucleic acid is heterologous".

Thus, Applicants submit that the claims, as amended, even more particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Reconsideration and withdrawal of rejections and respectfully requested.

Rejection of Claims 7-9, 12-14, 16-18, 20-22 and 44-46 Under 35 U.S.C. §112, First Paragraph

Claims 7-9, 12-14, 16-18, 20-22 and 44-46 are rejected as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

A) The Examiner rejected Claims 7-9, 14, 18 and 22 as drawn to nucleic acid molecules which encode CD2BP2 protein from a substantial variety of species. The Examiner stated that the specification did not adequately disclose a CD2BP2 from any species other than human.

Claims 7, 9, and 22 have been amended to recite "a protein of SEQ ID NO: 2".

B) The Examiner rejected Claims 7-9, 14, 18 and 22 with regard to polypeptide fragments that have CD2BP2 protein activity. The Examiner stated that, with the exception of the fragments of CD2BP2 that contain a CD2-interaction motive (SEQ ID NO: 3 or SEQ ID NO: 9), nucleic acid molecules which encode a fragment of CD2BP2 having said protein activity are not adequately described.

Claims 7, 8, and 22 have been amended to recite "wherein said fragment has biological activity of polypeptides of SEQ ID NO: 3 or SEQ ID NO: 9" in reference to a fragment of a human protein of SEQ ID NO: 2. Claims 9, 14, and 18 are dependent on Claim 7.

C) and D) The Examiner rejected Claims 7-9, 14, 18 and 22 as drawn to nucleic acids that encode active derivatives of CD2BP2 that have CD2BP2 protein activity or protein derivatives that have substantial sequence identity with SEQ ID NO: 22.

Claims 7, 8, and 22 have been amended to delete references to "derivatives" and to specify the requisite sequence identity.

E) The Examiner rejected Claims 7-9, 11-13, 15-17, 19-21, and 45-46 as encompassing subject matter that is not adequately described by the disclosure. The Examiner indicates that the rejection is due to open-language interpretation of nucleic acid molecules *comprising* nucleotide sequences encoding either a fragment of CD2BP2 (Claims 7-9) or amino acid sequences SEQ ID NO: 9 and 10 (Claims 12-13). The Examiner seemed to suggest that these claims should be interpreted as drawn to an indeterminate number and types of nucleotides, since any nucleotide in addition to the recited sequences is not excluded.

Applicants respectfully disagree. Where, as here, (1) the inventive portion of the subject matter is disclosed (sequences defined by their SEQ ID NOS, ORFs, etc.) and (2) any additional variability within the genus arises due to addition of elements that are not part of the inventor's

contribution, and when the level of knowledge and skill in the art would allow one skilled in the art to recognize that the applicant was in possession of the genus, the written description cannot be deemed defective.

The specification discloses the sequences referred to in the claims, and the level of the knowledge in the art would allow a skilled practitioner to either chemically or enzymatically synthesize nucleic acid molecules of the present invention, regardless of the variability in the additional, non-excluded nucleotides. Therefore, a skilled practitioner must conclude that the inventors had possession of the claimed invention at the time the invention was made.

Reconsideration and withdrawal of rejection are respectfully requested.

Rejection of Claims 7-9, 12-14, 16-18, 20-22 and 44-46 Under 35 U.S.C. §112, First Paragraph

Claims 7-9, 12-14, 16-18, 20-22, and 44-46 are rejected because the specification, the Examiner alleges, does not reasonably provide enablement for the scope of the claims as requiring undue experimentation.

A) The Examiner stated that Claims 7-9, 14, 18, and 22 encompass a CD2BP2 protein, or a functional fragment thereof, from *any* species, while only CD2BP2 of *human* derivation is disclosed. The Examiner further stated that it would require undue experimentation for one skilled in the art to make an isolated nucleic acid which encodes a CD2BP2 protein, other than one derived from human.

Claims 7, 9, and 22 have been amended to recite "a protein of SEQ ID NO: 22". Claims 8, 14, and 18 are dependent on Claim 7.

B) The Examiner rejected Claims 7-9, 14, 18 and 22 as drawn to nucleic acids that encode any fragments of CD2BP2 that have CD2BP2 protein activity. The Examiner contends that, with the exception of the fragments of CD2BP2 that contain a CD2-interaction motif (SEQ ID NO: 3 or SEQ ID NO: 9), nucleic acid molecules which encode any fragment of CD2BP2 having said protein activity would require undue experimentation for one skilled in the art to make and isolate.

Applicants respectfully disagree. The full sequence of CD2BP2 is disclosed. Examples of contemplated biological activities are provided on page 28, lines 10-12. Methods for assessing said activities are either exemplified in the disclosure (page 11, line 25 through page 12, line 4 and page 12, line 13 through page 13, line 19) or well established in the art. Thus, a skilled practitioner is fully enabled to find *any* functional fragment of CD2BP2 without undue experimentation.

However, in the interest of expediting prosecution, Claims 7, 8, and 22 have been amended to recite "having a biological activity of polypeptides of SEQ ID NO: 3 or SEQ ID NO: 9" in reference to a fragment of a protein of SEQ ID NO: 2. Claims 9, 14, and 18 are dependent on Claim 7.

C) The Examiner rejected Claims 7-9, 14, 18 and 22 as drawn to nucleic acids that encode any active derivative of CD2BP2 that has CD2BP2 protein activity because, the Examiner states, nucleic acid molecules which encode any active derivative of CD2BP2 having said protein activity would require undue experimentation for one skilled in the art to make and isolate.

Claims 7-9, 14, 18, and 22 have been amended to delete references to a "derivative".

D) The Examiner rejected Claim 8, drawn to a nucleic acid molecule encoding a derivative possessing a substantial sequence identity with CD2BP2, because, the Examiner states, it would require undue experimentation for one skilled in the art to make such a molecule.

Claim 8 has been amended to recite the phrase "sequence identity of at least 80%" in reference to a nucleic acid. Page 27, lines 1-5 recites preferred ranges of the "sequence identity"; lines 14-27 describe the algorithm for ascertaining said sequence identity. Claim 8 has been further amended to delete a reference to a "derivative". Applicants submit that the reference to a functional algorithm coupled with the definition of the "sequence identity" adequately define, describe and enable one skilled in the art to practice the invention of Claim 8.

E) The Examiner rejected Claims 7-9, 11-13, 15-17, 19-21, and 45-46 as encompassing subject matter that is not enabled as requiring undue experimentation to practice. The Examiner indicated that the rejection is due to open-language interpretation of nucleic acid molecules *comprising* nucleotide sequences encoding either a fragment of CD2BP2 (Claims 7-9) or amino acid sequences SEQ ID NO: 9 and 10 (Claims 12-13, 16-17, and 19-21), and that these claims would be interpreted as drawn to an indeterminate number and types of nucleotides, since any nucleotide in addition to the recited sequences is not excluded. The Examiner indicates that the quantity of experimentation necessary, the unpredictability of the art, and the alleged lack sufficient guidance do not enable one skilled in the art to practice the claimed invention.

Applicants respectfully disagree. The specification discloses the sequences referred to in the claims, and the level of the knowledge in the art would allow a skilled practitioner to either chemically or enzymatically synthesize nucleic acid molecules of the present invention, regardless of the variability in the additional, non-excluded nucleotides. Additional nucleic acid sequences joined to the recited molecule are mere optimization and depend on the particular use of the invention. Such optimization is well within the skill in the art. Therefore, a skilled practitioner must conclude that no undue experimentation is required to practice the claimed invention.

Reconsideration and withdrawal of rejection are respectfully requested.

Rejection of Claims 13, 17 and 21 Under 35 U.S.C. §102(b) over Seed *et al.*

Claims 13, 17, and 21 are rejected under 35 U.S.C. §102(b) as anticipated by Seed *et al.*, "Molecular cloning of the CD2 antigen, the T-cell erythrocyte receptor, by a rapid immunoselection procedure", Proc. Natl. Acad. Sci. USA, 84(10):3365-3369 (1987), hereinafter "Seed".

Seed discloses an isolated nucleic acid that encodes the amino acid sequence of CD2 protein; the sequence encompasses SEQ ID NO: 10.

Claim 13 has been amended to recite "consisting of", as suggested by the Examiner. Claims 17 and 21 are dependent on Claim 13. Reconsideration and withdrawal of rejection are respectfully requested.

Rejection of Claims 12, 16 and 20 Under 35 USC §102(b) over Percy

Claims 12, 16, and 20 are rejected under 35 USC §102(b) as anticipated by the results of NCBI BLAST search, submitted to the EMBL data library in October 1996 by Percy, C. (hereinafter "Percy").

Percy teaches a nucleotide sequence derived from *C. Elegans*, wherein nucleotides 19-45 of the disclosed sequence are encompassed by SEQ ID NO: 9 of the instant invention.

Claim 12 has been amended to recite "consisting of", as suggested by the Examiner. Claims 16 and 20 are dependent on Claim 12. Reconsideration and withdrawal of rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Alexander Akhiezer

Alexander Akhiezer
Registration No. P-54,617
Telephone (978) 341-0036
Facsimile (978) 341-0136

Concord, Massachusetts 01742-9133, U.S.A.

Dated: 6-30-03

MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 14, line 26 through page 15, line 24 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The CD2BP2 molecule has several unique features that distinguish it from SH3 and WW domain-containing proteins. Although there is some difference in their detailed specificity, SH3 and WW domains both bind to PxxP-containing sequences. Consistent with this specificity, CD2-binding proteins with SH3 domains have been reported, and it has been determined that they mostly bind to the PPLP (SEQ ID NO: 11) sequence (amino acids 302-305 in Fig. 3B), which is an SH3 ligand consensus site (Bell *et al., J. Exp. Med. 183*:169-178 (1997); Gassmann *et al., Eur. J. Immunol. 24*:139-144 (1994)) within the most highly conserved portion of the CD2 tail segment. In contrast, CD2BP2 binds to a site containing the two tandem PPPGHR (SEQ ID NO: 10) motifs but not to the SH3 ligand consensus sites (Fig. 3B). Moreover, unlike SH3 domains whose ligands require only eight residues for binding (Ren *et al., Science 259*:1157-1161 (1993); Musacchio *et al., Prog. Biophys. Mol. Biol. 61*:283-297 (1994)), CD2BP2 requires a 21-residue segment. It is believed that this CD2BP2 binding segment transiently assumes a configuration necessary for interaction, perhaps regulated by divalent cations. Conservation of the dibasic residues within the two tandem motifs, including the histidine in human, mouse, rat, and horse CD2, is noteworthy. It has previously been shown that the PPPGHR (SEQ ID NO: 10)-containing region of the CD2 tail is essential for CD2 ectodomain-stimulated IL-2 production (Chang *et al., J. Exp. Med. 169*:2073-2083 (1989); Chang *et al., J. Exp. Med. 172*:351-355 (1990)). Although the mechanism by which the tandem PPPGHR (SEQ ID NO: 10) sequences trigger IL-2 gene activation on CD2 clustering is still unclear, it is possible that this region is needed for the proper orientation and/or function of the downstream SH3 ligand binding motif. Consistent with

this notion, replacement of the dibasic HR residues of the PPPGHR (SEQ ID NO: 10) segment with DE residues weakens not only the binding of CD2BP2 to this region but also that of the SH3 domain of $p59^{fyn}$ to the downstream SH3 consensus site. Thus, it is believed that CD2BP2 may play a biologic role in coordinating the binding of other interactors to the more C-terminal region of the CD2 tail.

Replace the paragraph at page 15, line 24 through page 16, line 17 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

SH3 domains are made up of 5-6 antiparallel β-strands forming a compact, barrel-like structure. As shown by analysis of complexes of SH3 domains and their ligands, the ligand for a given SH3 domain forms a left-handed polyproline-type II helix whose interactions with the SH3 domain are mediated primarily by hydrophobic residues within the binding site (Ren *et al., Science 259*:1157-1161 (1993); Musacchio *et al., Prog. Biophys. Mol. Biol. 61*:283-297 (1994)). WW domains form a three-stranded antiparallel β-strand with one of the two conserved tryptophan residues crucially involved in the interaction with the proline-rich ligand (Macias *et al., Nature 382*:646-649 (1996)). The *in vivo* binding assays described herein show that a number of aromatic residues of CD2BP2 probably are involved directly in the interaction with the proline-rich sequence motif of the CD2 cytoplasmic domain. However, structure-prediction methods and initial Nuclear Overhausen Effect (NOE) analysis indicate the presence of a central α-helix within the binding domain of CD2BP2 (residues 301-311). This helix is predicted to reside within the conserved 17-amino acid sequence shown herein to be necessary for the binding of the proline-rich ligand. It therefore appears that the binding domain of CD2BP2 defines a class of proline-rich recognition domains. In this fold, an α-helical rather than a β-strand structure displays those aromatic and hydrophobic residues necessary for the binding to the proline-rich ligand. Given that the CD2BP2 protein involved in binding to the PPPGHR (SEQ ID NO: 10) motif is expressed in different tissues, and that there is conservation of the GP[Y/F]xxxx[M/V]xxWxxxGYF (SEQ ID

NO: 9) sequence in other unrelated proteins derived from different species, it is likely that this interaction is not restricted to lymphocytes, but rather represents a basis for protein-protein interaction.

Replace the paragraph at page 19, line 4 through page 20, line 2 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Close inspection of the ligand binding site of the CD2BP2 GYF domain shows it to display a slightly bent, relatively smooth surface (Fig. 8A). A proline-rich ligand might be anticipated to bind along the axis defined by the α-helical residues of the binding site. Since four residues of the sequence PXXP (Pawson, *Nature 373*:573-580 (1995)) are able to adopt a proline-helical conformation, the PPPP (amino acids 1-4 or 15-18 of SEQ ID NO: 22) sequence of the PPPPGHR (amino acids 1-7 or 15-21 of SEQ ID NO: 22) repeat could assume such a conformation as well. Fig. 8B shows the surface area occupied by the conserved residues of the homology region of the GYF domain. Except for Y6, which is largely buried in the core of the protein, this area forms a subset of the contiguous surface of the whole binding site of the CD2BP2 GYF domain (Fig. 8A and 8B in comparison). We suggest that the conserved hydrophobic patch defines the major binding surface interacting with proline-rich ligands. This is likely to be the case for CD2BP2 as well as for all the other proteins containing the homology region of the CD2BP2 GYF domain (Fig. 6). We speculate furthermore that, since only 6-8 residues can be placed along this hydrophobic patch, one of the two proline-rich repeats in the CD2 tail is primarily responsible for the binding to the conserved residues of the homology region. In agreement with this hypothesis, the arrangement of two tandem PPPPGHR (amino acids 1-7 or 15-21 of SEQ ID NO: 22) segments seems to be a peculiarity of the CD2 cytoplasmic domain, since a Ψ-BLAST sequence search (Altschul, *et al., Nucleic Acids Res. 25*:3389-3402 (1997)) revealed no significant homology to the PPPPGHRSQAPSHRPPPPGHR (SEQ ID NO: 22) sequence found in CD2. In addition, the distribution of charged residues within the homology region is different for each of

the proteins compared in Fig. 6, implying that charged interactions might not be a conserved feature of the homology region containing proteins. In the case of the CD2BP2 GYF domain, however, E31 and D36 are part of the NMR mapped binding site and an number of additional negatively charged residues are located at the edge of the binding surface (Fig. 8C). No positive charge is present on this surface, suggesting that only acidic residues confer specificity to the interaction with the CD2 cytoplasmic domain, probably by interacting with the HR residues of the PPPPGHR (amino acids 1-7 or 15-21 of SEQ ID NO: 22) sequence.

Replace the paragraph at page 20, line 3 through page 21, line 2 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The fold of the GYF domain is unrelated to the structures of SH3 (Musacchio, *et al., Nature 359*:851-855 (1992); Yu, *et al., Science 258*:1665-1668 (1992)) or WW (Macias, *et al., Nature 382*:646-649 (1996)) domains, which display the side-chains for the interaction with the proline-rich ligand by means of β-strands and β-strand connecting loops. Nonetheless, there are some features shared between all three protein modules. For example, conserved hydrophobic residues line up to create a contiguous surface stretch. These residues define the axis for the binding of the proline-rich ligand in the case of SH3 and WW domains and we suggest this to be the case for the GYF domain as well. Second, glutamine or asparagine side-chains within SH3 and WW domains contribute to the interaction with the respective peptides by the potential formation of hydrogen bonds (Macias, *et al., Nature 382*:646-649 (1996); Musacchio, *et al., Prog. Biophys. Mol. Biol.* 61:283-297 (1994)). In the case of the GYF domain the side-chain amide protons of Q48 become largely shifted upon addition of the proline-rich ligand (Nishizawa, *et al., Proc. Natl. Acad. Sci. USA 95:*14897-14902 (1998)), indicating a direct interaction with the ligand. Third, a specificity pocket within SH3 and WW domains interacts with non-proline residues of the ligand, restricting the promiscuity of these domains. The surface properties and charge distribution of the GYF domain

binding site also argues for the necessity of non-proline residues to be present in the ligand for an optimal interaction. Residues E31 and Y33 extrude significantly from the surface, creating a wall at the C-terminal end of the α-helix. In order to interact with residues of the α-helix as well as the site defined by W8 and its spatially adjacent residues, one or more non-proline residues probably have to allow the ligand to bent around these extruding side-chains. The presence of a glycine residue within the PPPPGHR (amino acids 1-7 or 15-21 of SEQ ID NO: 22)-recognition motifs could provide this conformational flexibility within the ligand. Finally, the N– and C-terminus of all three domains are close in space. This facilitates the ability of SH3 and WW domains to function as universal protein-protein interaction modules present in many proteins involved in signal transduction. A similar adapter function might be anticipated for the GYF domain.

Replace the paragraph at page 27, lines 14 through 27 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin *et al.*, *Proc. Natl. Acad. Sci. USA*, *90*:5873-5877 (1993). Such an algorithm is incorporated into the NBLAST program which can be used to identify sequences having the desired identity to nucleotide sequences of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, *Nucleic Acids Res, 25*:3389-3402 (1997). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., NBLAST) can be used. [See http://www.ncbi.nlm.nih.gov.] In one embodiment, parameters for sequence comparison can be set at W=12. Parameters can also be varied (e.g., W=5 or W=20). The value "W" determines how many continuous nucleotides must be identical for the program to identify two sequences as containing regions of identity.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

Each amended claim marked up to show by way of bracketing and underlining the changes made relative to the previous version of each claim, and include the parenthetical expression to indicate the status of each claim (e.g., "(Amended)", "(Twice Amended)", etc.).

7. (Amended) An [I]isolated nucleic acid molecule which encodes a [CD2BP2] protein comprising SEQ ID NO: 2, or [an active derivative or] a fragment of said protein having [CD2BP2 protein] biological activity of polypeptides of SEQ ID NO: 3 or SEQ ID NO: 9, or the complement of said nucleic acid molecule.

8. (Amended) An [I]isolated nucleic acid molecule possessing sequence identity of at least 80% with the nucleic acid molecule of Claim 7, wherein said nucleic acid molecule encodes a fragment of a [the CD2BP2] protein of SEQ ID NO: 2 [is a derivative possessing substantial sequence identity with SEQ ID NO: 2] and wherein said fragment has biological activity of polypeptides of SEQ ID NO: 3 or SEQ ID NO: 9, or the complement of said nucleic acid molecule.

9. (Amended) An [I]isolated nucleic acid molecule of Claim 7, wherein said nucleic acid molecule has the same nucleotide sequence as [the] an endogenous gene encoding a [CD2BP2] protein of SEQ ID NO: 2.

10. (Amended) An [I]isolated nucleic acid molecule of Claim 7, wherein said nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:1.

11. (Amended) An [I]isolated nucleic acid molecule [consisting essentially of] comprising a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 3.

12. (Amended) An [I]isolated nucleic acid molecule consisting [essentially] of a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 9.

13. (Amended) An [I]isolated nucleic acid molecule consisting [essentially] of a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 10.

22. (Amended) A method for preparing a [CD2BP2] protein of SEQ ID NO: 2, or [an active derivative or] a fragment thereof, wherein said fragment has biological activity of polypeptides of SEQ ID NO: 3 or SEQ ID NO: 9, comprising culturing the recombinant host cell of Claim 18.

44. (Amended) An isolated recombinant nucleic acid molecule comprising a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 3, wherein [said nucleic acid molecule does not naturally comprise] said nucleotide sequence is heterologous.

45. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 9, wherein [said nucleic acid molecule does not naturally comprise] said nucleotide sequence is heterologous.

46. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 10, wherein [said nucleic acid molecule does not naturally comprise] said nucleotide sequence is heterologous.